Remarks/Arguments

Prior to the present amendments, claims 43-81 were pending in this application. Claims 61 and 81 have been canceled, claims 43, 60, 63 and 80 have been amended. The amendments are fully supported by the specification as originally filed, and do not add new matter. All amendments and cancellations are made without prejudice or disclaimer. Applicants explicitly reserve the right to pursue any deleted subject matter in one or more continuing applications.

Telephone Interview

During a telephone conference with the Examiner on August 5, 2008, the undersigned attorney confirmed the election, without traverse, of Group 5, claims 43-60 and 62-81, concerning a method for treating central nervous system cancer. The Examiner indicated that the Office Action mailed on May 7, 2008 would be vacated, and a new Office Action would be issued on the claims of the elected invention.

Election Requirement

Applicants note and appreciate the Examiner's decision to rejoin the claims of Group 5 and Group 11. Accordingly, claims 43-81 are under examination in the present application to the extent that they concern treatment of central nervous system cancer or glioma cells, using an antibody that binds to SEQ ID NO: 2. The foregoing amendments serve to limit the claims to the elected invention.

Claim Rejections – 35 USC § 112, First Paragraph, Enablement

(1) Claims 43-81 were rejected under 35 U.S.C. 112, first paragraph as allegedly failing to comply with the enablement requirement. According to the rejection, the specification "does not have any data or objective evidence that central nervous system cancer or gliomas could be successfully killed or treated using an antibody to SEQ IDNO:2, including its Fc variant," and the "specification does not have any data or objective evidence that cancers in the central nervous system other than glioma overexpress SEQ ID NO: 2" (Office Action, page 4).

In support of the rejection, the Examiner (citing While et al., *Ann Rev Med* 52:125-145, 2001) argues that immunotherapy of cancer is highly unpredictable, and adds (citing Roopenian et al., *Nature Reviews, Immunology*, 7:715-723, 2007) that this is especially true for brain cancer, in view of difficulties posed by the blood-brain barrier. The Examiner cites Boon, *Adv Can Res* 58:177-210, 1992, as allegedly teaching that cancer tolerance and loss of tumor antigen may interfere with antibody treatment of cancer. Kirkin et al., APMIs, 106:665-679 (1998) is cited as allegedly teaching that although several peptides of melanoma associated antigens have been identified, only one has shown to have limited anti-tumor activity. Smith, *Clin Immunol* 41(4):841-849 (1994), is relied on for its alleged teaching that antigen overload, due to antigen shedding, by actively growing tumor, could block specifically cytotoxic or proliferative responses of tumor specific T cells. Bodey et al., *Anticancer Res* 20:2665-2676 (2000) is cited for its alleged teaching of reasons for failure of cancer vaccines. Lee et al., *J Immunol* 163:6292-6300 (1999) is cited for its alleged teaching that T-cell specific immune response in melanoma patients does not associate with regression of metastatic melanoma. Kaiser, *Science* 313:1370 (2006) is relied on for its statement that 90% of tumor drugs fail in patients. Ezzel, *J NIH Res* 7:46-49 (1995) is relied on as a further reference allegedly expressing doubts about the efficacy of cancer vaccine approach.

The Examiner adds that even if treatment of glioma were enabled, one cannot predict that other cancers in the central nervous system overexpress the polypeptide of SEQ ID NO: 2.

Claims 61 and 81 have been canceled; the rejection of the remaining claims is respectfully traversed.

A prima facie case of lack of enablement has not been established

"In order to make a rejection [under the enablement prong of 35 USC 112, first paragraph], the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." MPEP § 2164.04 Such reasonable basis has not been provided in the present case.

The Examiner cites a variety of unrelated documents, most of which are not relevant to the issue of enablement in the present case, since they are outdated (published 8-6 years before the priority date of the present application) and/or concern approaches to cancer treatment, such as cancer vaccines, that are entirely different from the approach disclosed and claimed in the present application. Furthermore, most arguments advanced by the Examiner do not specifically address the question while the particular methods claimed in the present application, as opposed to cancer treatment in general, would not be expected to work. Indeed, the efficacy of therapeutic antibodies is clearly demonstrated by the wide-spread successful use of antibody therapy in the treatment of a variety of cancers, including severe, aggressive forms of cancer, and the fact that currently there are twenty-one FDA approved therapeutic monoclonal antibodies in the U.S. market and hundreds of more are undergoing clinical trials. The fact that not all clinical trials are successful is irrelevant for the assessment of patentability, since the legal standard for assessing patentability is not absolute certainty rather preponderance of evidence.

The Examiner completely failed to address while the methods claimed in claims 43-60 and 62, which are not directed to therapeutic treatment, would not be enabled.

Even if a prima facie case of obviousness had been established, the rejection should be withdrawn in view of the following arguments and evidence

The polypeptide of SEQ ID NO: 2, designated in the present application as "TAT4434," is also known as beta2-microglobulin, which, as attested by the enclosed printout, is present in the NCBI protein database under accession no. NP_004039. The present application shows that TAT4434 (beta2-microglobulin) nucleic acid is overexpressed in gliomas related to normal brain tissue (see Example 3). The present claims are based on this finding, which indicates that TAT4434 of SEQ ID NO: 2 can be used as a target for tumor treatment, using anti-TAT4434 antibodies, as disclosed in the specification. Anti-TAT4434 antibodies may be effective alone or as targeting agents to direct cytotoxic agents or chemotherapeutic drugs to the tumor site (see, e.g. claims 47-52 and 67-72).

The ability of anti-TAT4434 (anti-beta2-microglobulin) antibodies is supported by several post-published documents, copies of which are enclosed. These documents show that

beta2-microglobulin has oncogenic activity and that targeting the protein with antibodies can kill tumor cells.

Thus, Huang et al., *Cancer Res* 66(16):9108-9116 (2006), is involved in and "is an attractive target for the treatment of lethal prostate cancer bone metastasis" (abstract, final sentence).

Nomura et al., *The Journal of Urology* 178:292-300 (2007), examined the effects of an anti-beta2-microglobulin antibody on renal cell carcinoma cell growth and apoptosis in vitro and found that anti-beta2-microglobulin antibody treatment strongly suppressed cancer cell growth. The authors concluded that targeting beta2-microglobulin mediated signaling was a novel therapeutic approach for human renal cell carcinoma.

Yang et al., *Blood* 110(8):3028-35 (2007), report that anti-beta2-microglobulin monoclonal antibodies induce apoptosis in myeloma cells, and conclude that the data "provides strong evidence to support the potential of these mAbs as therapeutic agents for myeloma" (abstract, final sentence).

Huang et al., *Clin Cancer Res* 14(17):5341-7 (2008), report that beta2-microglobulin signaling blockade with an anti-beta2-microglobulin antibody caused apoptosis in human prostate cancer cells.

This post-published evidence confirms that antibodies to TAT4434 of SEQ ID NO: 2 (beta2-microglobulin) effectively kill cancer cells expressing beta2-microglobulin. This, coupled with the experimental data disclosed in the present application, clearly enables the killing of central nervous system cancer cells that express such polypeptide (e.g. glioma cells), and the treatment of tumors comprising such cells, as claimed in the present application. This is true despite difficulties associated with delivery of drugs through the blood-brain barrier, since various approaches for drug delivery through the blood-brain barrier, such as osmotic and biochemical means, and the use of vasoactive substances, are well known in the art.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claims 43-81 were rejected under 35 U.S.C. 112, first paragraph for alleged lack of enablement for treating central nervous system cancer or glioma using an antibody to a polypeptide having at least 80% identity to SEQ ID NO: 2. The Examiner asserts that it is unpredictable if a polypeptide having 80% sequence identity to SEQ ID NO: 2 would have the same properties and the polypeptide of SEQ ID NO: 2, and if it would overexpress in central nervous system cancer or gliomas as compared to normal brain tissue.

Claims 61 and 81 have been canceled. The rejection of the remaining claims is respectfully traversed.

The claims, as currently amended, cover methods targeting variants of SEQ ID NO: 2 which are overexpressed in central nervous system or glioma cancer cells relative to corresponding normal cells. Accordingly, the withdrawal of the present rejection is respectfully requested.

(3) Claims 56-59 and 76-79 were rejected under 35 U.S.C. 122, first paragraph for alleged lack of enablement for making an antibody that has increased binding to FcRn, using any amino acids recited in claims 56 or 76.

The rejection is respectfully traversed.

As disclosed in the present application, under the heading Effector Function Engineering:

> "Modifications of specific residues within the human IgG1 Fc region previously have been shown to enhance binding to specific receptors, e.g., the human FcRn receptor. Shields et al., J. Biol. Chem., 276:6591-6604 (2001). FcRn, the neonatal Fc receptor, is an Fc receptor which is structurally similar to the major histocompatability complex (MHC) and consists of an .alpha-chain noncovalently linked to .beta2-microglobulin. FcRn is thought to be involved in IgG transport and clearance. Rhagavan et al. Annu. Rev. Cell Dev. Biol., 12:181-220 (1996). The FcRn complex has the property of binding the Fc region of IgG at acidic pH (about 6.0-6.5) and not at neutral pH. Known functions of FcRn are transplacental transfer of IgG during fetal development, transfer of IgG across the neonatal gut,

and prolongation of the half life of circulating IgG via recycling the IgG from endocytic vessels back into the circulation. In each case, FcRn binds IgG at acidic pH, then carries the IgG to a different compartment where it is released at neutral pH."

Methods for generation of amino acid variants at the indicated positions of an antibody Fc region, such as targeted random motagenesis, were well known in the art at the priority date of the present application. Similarly, methods for assessing the binding of such variants to FcRn, such as competitive FACS binding assays, were well known, along with methods for measuring the half-life of antibodies comprising such alteration within their Fc region.

Based on this teaching and general knowledge in the art at the priority date of the present application about effector function engineering of antibodies, one of ordinary skill in the art would have been able to engineer the effector function of the antibodies used in the methods of the present invention by amino acid alterations at one or more positions recited in the claims, without undue experimentation. It is noted that the fact that some, or even extensive, experimentation might be necessary, should not lead to the finding of lack of enablement, if it is of routine nature, as it is in the present case.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

CONCLUSION

All claims pending in this application are believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, or credit overpayment to Deposit Account No. **50-4634** (referencing Attorney's Docket No. **GNE-0294R1 (123851-181649)**).

Respectfully submitted,

Date: February 4, 2009

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